DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20014

NATIONAL CANCER INSTITUTE

October 23, 1973

TO: Screeners, Suppliers and Staff

FROM: Acting Head, Automated Information Section
Drug Evaluation Branch, DR&D, DCT, NCI

SUBJECT: Change in method of calculating median survival time

The Drug Evaluation Branch has decided to change the method for calculating median survival time from the one outlined in Protocol 11.200 to the one outlined in this instruction. This method has been recommended by Dr. Irwin Miller of Arthur D. Little, Inc. and some of his original comments are attached.

Our computer programs are currently being modified to perform the median calculation considering the mortality data as grouped rather than ungrouped. We will not be recalculating our historical data. Median survival time and T/C% is calculated exclusively by computer program. The purpose of this instruction is to familiarize receivers of Screening Data Summaries with the change in method so that data may be examined more intelligently.

The revised formula is:

$$L + cj/f_M$$

where L is the lower boundary of the class (day) containing the median animal, c is the class interval (always 1 day in our case), j is the number of deaths needed to reach the median animal in the median class, and $f_M$ is the number of deaths in the median class.

## INTRODUCTION

We have observed that various laboratories use different methods to calculate medians. Since this lack of uniformity contributes unnecessarily to variability in T/C values, we have given careful consideration to the best method for computing the median survival time from a statistical point of view.

In this memorandum we describe a recommended method for computing the median survival time. We also discuss the statistical and philosophical background for this method, and we give examples which show how it is used.

## BACKGROUND

In statistics, medians are computed in distinct ways for grouped and for ungrouped data. For ungrouped data (where all the individual values are available) the median for an odd number of observations is the middle number. If we have an even number of observations, the median is the average of the two "middlemost" observations.

For grouped data, the median is computed in the following manner. The observations are grouped into classes with lower and upper boundaries. The median of a set of grouped data is given by the lower boundary of the class into which the median must fall plus a fraction of its class interval, which depends on the number of items we still lack when reaching this lower boundary. Thus, the formula for computing the median for grouped data is:

$$M = L + c \cdot \frac{j}{f_M}$$

where L is the lower boundary of the class containing the median, $f_M$ is the frequency of that class, c is the class interval, and j is the number of items we still need to reach the median.

Currently, most screening labor atories are computing medians as if the data were ungrouped. However, we take the strong view that survival data are actually grouped data. If a mouse is said to die on day 9, in fact, the mouse belongs to a group that died after day 8 and before day 10. Day 9, then, is not an individual observation, but represents a class of observations falling within the 24-hour period between day 8 and day 10. Thus, data on mouse survival are automatically grouped into classes having a common class interval of 24 hours.

The following three-step procedure for determining the median survival time is recommended:

a. Locate the median class (the day containing the median animal).

b. Determine what proportion of the median class is needed to needed to reach the "middlemost" animal.

c. The median is the lower class boundary of the median class plus the needed proportion times the class interval.

EXAMPLES

1. Even Number of Animals

Suppose a control group of 30 animals had the following distribution of days to death:

day 9: 14 animals

day 10: 16 animals

a. Since there is an even number of animals (30), there are two middlemost animals (the 15th and 16th to die). The class containing both these animals is called "day 10."

b. The"middlemost" animal is the $\frac{15+16}{2}$ = 15.5th animal to die. Since 14 animals died in the class "day 10." Thus, we need the

fraction $\frac{1.5}{16}$ = 0.09 of the 16 animals in the median class.

c. The lower class limit for the median class is 9.5. Thus, the median survival time is 9.5 + 0.09 = 9.6 days (rounded to one decimal place).

2. Odd Number of Animals

Consider a control group of 33 animals whose deaths have the following distribution:

day 8: 5

day 9: 11

day 10: 17

The median survival time is computed to be:

$$9.5 + \frac{1}{17} = 9.5 + .06 = 9.56 \text{ or } 9.6 \text{ days.}$$

If we had computed the median as if the data were ungrouped, we would have obtained 10 days, since the 17th mouse died in day 10. However, 16 mice died by day 9 and the 17th mouse died on day 10. In fact, the 17th mouse might have actually died only shortly after the 16th mouse, but because of the way deaths are observed and recorded, the reported difference appears to be an entire day. Thus, the result would have been 9 days, a full day different. Note that the result using the grouped-data method would have hardly changed at all if one mouse died on another day.

3. Test Group of 6 Animals

Suppose the deaths have the following distribution:

day 10: 2

day 11: 2

day 13: 1

day 14: 1

$$\text{Median survival time} = 10.5 + \frac{1.5}{2} = 10.5 + .75 = 11.25$$

## CONCLUSIONS

When we treat survival time as grouped data, we reduce the inherent variability of our measurements (T/C's). Example 2 shows that this method is not nearly as sensitive to the day of death of a single animal as the ungrouped-data method. With less inherent variability, presumed activity/toxicity limits can be tightened with no loss in reproducibility.

The grouped-data method is not difficult to apply. The examples show that a few more calculations are required. However, the additional calculations take little additional time, and they can easily be programmed for the computer. We feel that the statistical correctness of the method more than justifies the minor additional work required to perform the calculations.

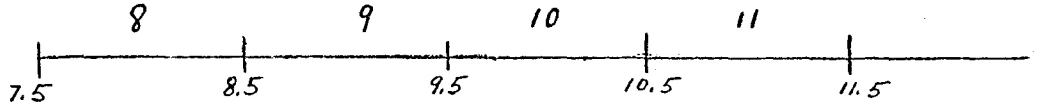
Recently, a screening laboratory found a known active compound inactive in the mini-screen feasibility experiment, while we concluded that the compound is active. The laboratory used the ungrouped method for calculating median survival time, obtaining a T/C of 120%; we used the grouped method, obtaining 125%. The compound was MTX, a known active compound against the L1210 tumor system.

# CHANGE OF METHOD FOR CALCULATING MEDIAN SURVIVAL TIME

I. Preliminary Information

1) Figure each day as lower limit boundary and upper limit boundary

ie day 9 = 8.5 to 9.5
day 10 = 9.5 to 10.5
day 11 = 10.5 to 11.5




2) Determine the median animal in each group

ie

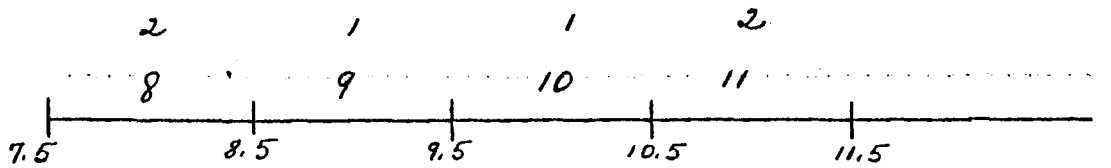
| number of mice | median mouse |
|---|---|
| 3 | 2 |
| 6 | $\frac{3+4}{2} = 3.5$ |
| 10 | $\frac{5+6}{2} = 5.5$ |
| 33 | 17 |

3) Object: Determine when that middle (median) animal died.

Procedure:

1) ie 6 mice -
where does 3.5 mouse die?

| day | deaths |
|---|---|
| 8 | 2 |
| 9 | 1 |
| 10 | 1 |
| 11 | 2 |




By the end of the 9th day (9.5) 3 mice have died - you need to know 3.5 so you are still .5 mouse short - that .5 occurred in day 10 -

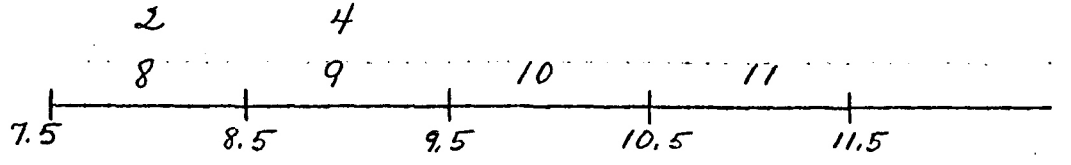
so $\frac{.5}{1}$ → amount needed / number of mice that died on day 10 = .5

MST = 9.5 + .5 = 10

Another example:

2) Total 6

| day | deaths |
|---|---|
| 8 | 2 |
| 9 | 4 |




Again you need median animal, for 6 which is 3.5

By the end of the 8th day you have 2 mice - you need 3.5 - that occurs on the ninth day - now you are 1.5 mice short

$$\frac{1.5}{4} \quad \begin{matrix}\text{amount needed} \\ \text{total number of mice dead on that day}\end{matrix} \quad = .38$$

MST = 8.5 + .38 = 8.88 = 8.9

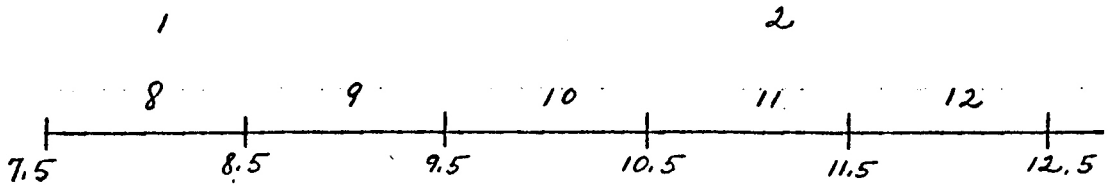
$$\text{MST} = \begin{matrix}\text{Lower limit of} \\ \text{day median animal} \\ \text{dies}\end{matrix} + \frac{\text{amount needed to reach median animal}}{\text{Total \# of animals that died on that day}}$$

III. Additional Examples

3 mice - median mouse is #2

Question - where does # 2 mouse die

| day | | deaths |
|---|---|---|
| 8 | = | 1 |
| 11 | = | 2 |




10.5 + 1/2 = 11 MST

day 9 = 3 8.5 + 2/3 = 8.5 + .67 = 9.2 MST

---

day 8 = 1 11.5 + 1/2 = 12.0 MST
day12 = 2

---

day 10 = 1 10.5 + 1/2 = 11.0 MST
day 11 = 2

---

day 8 = 1 MST = 11.5 10.5 + 1/1 = 11.5
day 11 = 1
day 14 = 1

---

day 14 = 3 13.5 + 2/3 = 13.5 + .67 = 14.2 MST

IV. Additional Information

1) The class interval "C" in L + cj/fm is a constant, (1 day) so it is dropped in these examples.

2) Remember the information recorded on the screening control record 1157, and screening test record 1158-2 is recorded as survivors, and this formula uses deaths.

(You may wish to record deaths above the boxes lightly in pencil initially for easier initial calculations.

add to lower class limit

MEDIAN SURVIVAL TIME

6 Animals

3 0 = .2

3 1 = .3

3 2 = .5

4 0 = .4

4 1 = .5

4 2 = .8

5 0 = .5

5 1 = .6

5 2 = .8

6 0 = .6

6 1 = .7

6 2 = .9

3 Animals

3 1 = .5

2 1 = 1

3 0 = .7

2 0 = .5

MEDIAN SURVIVAL TIME

10 Animals

5 0 = .1

5 1 = .1

5 2 = .2

5 3 = .3

5 4 = .5

6 0 = .3

6 1 = .3

6 2 = .4

6 3 = .5

6 4 = .8

7 0 = .4

7 1 = .4

7 2 = .5

7 3 = .6

7 4 = .8

8 0 = .4

8 1 = .5

8 2 = .6

8 3 = .7

8 4 = .9

9 0 = .5

9 1 = .6

9 2 = .6

9 3 = .8

9 4 = .9

10 0 = .6

10 1 = .6

10 2 = .7

10 3 = .8

10 4 = .9

# MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE

TO : All In Vivo Screeners

DATE: May 20, 1976

FROM : Head, Screening Section, DEB, DR&D, DCT, NCI

SUBJECT: Instructions for delayed drug treatment (i.e. any rodent model with the first drug treatment on or after day 3)

Parameter: Median (not mean) survival time.

Schedule:

Day 0 -- Implant tumor. Run bacterial cultures (see Protocol 7).

Day 1 -- Check cultures. Discard contaminated groups. Randomize animals.

Day 2 -- Recheck cultures. Cancel testing if contaminated.

Day of first drug injection -- Weigh animals (see Protocol 10). Treat as instructed, administering drug based on individual body weight. Record survivors daily.

Four days after first drug treatment -- Weigh animals for determination of weight change (see Protocol 4.301,b,3). If first drug treatment was day 3 or later the computer will calculate a T/C % regardless of the number of survivors on the acute toxicity day.

Day for Determination of control early-deaths - Temporarily half of the mid point of the acceptable control range. Chart is being prepared.

Day for Determination of survivors as cures, no takes, etc. is to be the day of final evaluation.

Initial drug treatment day must be the same for the complete experiment, including the positive control compound.